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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/099,895	03/14/2002	Mark Andrew Guthridge	3991/0K379US0	5422

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EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/099,895	GUTHRIDGE ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *73,75-77 and 79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73,75-77 and 79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 9/6/07 has been entered.

Status of Application, Amendments and/or Claims

The amendment of 9/6/07 has been entered in full. Claims 73, 75 and 79 are amended. Claims 74 and 78 are canceled. No new claims are added.

Claims 73, 75-77 and 79 are pending in the instant application.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (5/2/07).

The objection to the specification at pg 3 is *withdrawn* in view of Applicants' amendments to the specification.

All rejections of claims 74 and 78 are moot in view of Applicants' cancellation of these claims.

The rejection of claims 73, 75-77 and 79 under 35 U.S.C § 112, second paragraph, at pg 7-8 as being incomplete for omitting essential steps is *withdrawn* in view of Applicants' amendments to the claim 73. However, please note that claims 77 and 79 are newly rejected under 35 U.S.C. § 112, second paragraph for the reasons set forth below.

The rejection of claims 73, 75-77 and 79 under 35 U.S.C. § 102(b) as being anticipated by Smith et al (1997) is *withdrawn* in view of Applicants' amendments to the claims.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 73, 75-77 and 79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *in vitro* method of inhibiting hematopoietic cell survival comprising expressing a GM-CSF/IL-3/IL-5 receptor in an *in vitro* hematopoietic cell, wherein the receptor has a beta-chain having the amino acid sequence of SEQ ID NO: 1, wherein the amino acid sequence ^{598}HSRSLP^{603} of the beta-chain comprises one or more substitution mutations, the amino acid sequence ^{598}HSRSLP^{603} has a substitution mutation at the serine residue at position 601, and the expression of the mutant receptor inhibits survival of the hematopoietic cell, does not reasonably provide enablement for said method performed *in vivo* (e.g., wherein the hematopoietic cell is an *in vivo* hematopoietic cell). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This rejection was set forth previously and maintained at pg 4-7 of the 5/2/07 Office Action.

Applicants' arguments (9/4/07; pg 6-7) as they pertain to the rejection have been fully considered and are persuasive in part. Specifically, Applicants' arguments with respect to beta-chain variants encompassed by the claims are found to be persuasive, but Applicants' arguments with respect to *in vivo* methods of inhibiting hematopoietic cell survival are not found to be persuasive.

With respect to beta-chain variants, Applicants argue the claims have been narrowed "to set forth that the mutations are limited to receptors with a substitution mutation at Ser^{601}" (pg 6). Applicants further argue, "receptors with a beta-chain mutation S601G and beta-chain mutation RSL → AAA also exhibit apoptosis (see page 56, line 14 to page 57, line 2" of the 2/2/07 substitute specification (pg 6-7).

This portion of Applicants' arguments has been fully considered and is found persuasive. Specifically, Applicants' argument that the specification enables other mutations of the "binding motif" (residues 598-603) that include the substitution at Ser^{601} (e.g., the single residue mutant (S601G) and the triple residue mutant) is found persuasive. Therefore, the following statement set forth in the previous Office Action is withdrawn: "it is not predictable whether not changes that alter less than all six residues will also result in decreased cell survival" (pg 6). It is noted that mutation of Ser^{601} eliminate or reduce the function of the beta-chain; therefore, the skilled artisan would predict that additional mutations made to the beta-chain would not impact practice of the claimed method once the function of the beta-chain has been eliminated by substitution mutation of the S601G residue. As previously described, the prior art (Smith et al, 1997; cited previously) teaches that a truncated beta-chain ending at residue 541 (and thus missing residue 601) also fails to support growth of transfected cells.

With respect to a method of inhibiting cell survival *in vivo*, Applicants argue that "[i]t is not beyond the skilled addressee to predict or extrapolate from *in vitro* data to an *in vivo* situation" (pg 7). Applicants argue that undue experimentation is not required because of the "small genus of methods each requiring that the receptor contains a substitution mutation at Ser^{601}" and "methods to introduce the mutated sequence encoding the receptor are known in the art both in an *in vitro* and in an *in vivo* setting".

Applicants' arguments have been fully considered but are not found persuasive. It is acknowledged that the claims have been narrowed such that variant beta-chains encompassed by the claims are limited to those with a substitution mutation at Ser^{601}. This substitution mutation results in a non-functional beta-chain with respect to hematopoietic cell survival. However, the smaller number of variant beta-chains encompassed by the claims does not remove the burden of undue experimentation required by the skilled artisan prior to practicing the claimed method *in vivo*. As set forth previously, there are no working examples or other evidence in the specification indicating that the *in vitro* activity measured by the assay in Example 8 is predictive of *in vivo* activity. Even if the cell signaling transduction pathway may potentially be the same in each case, the extracellular conditions of cells grown *in vitro* (e.g., in culture) are very

different from the condition of cells grown *in vivo* (e.g., in an organism) and may effect the phenotype of cell survival in an unpredictable way. For example, both the instant specification (pg 45, lines 21-23) and the relevant art (Guthridge et al (2000); cited previously) teach that CTL-EN cells expressing the mutant receptor show no defect in cell survival when grown in 10% FCS (fetal calf serum). This example demonstrates that the survival of hematopoietic cells expressing the mutant receptor is sensitive to the environment (extracellular conditions).

Furthermore, the experimental conditions used the *in vitro* assays appear problematic to replicate *in vivo*. Specifically, in the experiments describe in the specification, human receptor comprising the wild type or mutant beta-chain was expressed in mouse cells (CTL-EN) also expressing the wild type mouse receptor. Selective activation (or lack thereof with the mutant beta-chains) of the receptor was achieved using human IL-3, with stimulation by murine IL-2 used as a control for cell survival. The skilled artisan would predict that this method would not work *in vivo* with said mutant human receptor due to the presence of native human receptor and native human IL-3. Thus, practicing the claimed method would require gene therapy that both knocks out expression of the native human receptor beta-chain (e.g. by using antisense nucleic acid sequences) and results in expression of the mutant receptor beta-chain in the target hematopoietic cells.

The *in vivo* methods encompassed by the claims include methods comprising administration of genetically altered hematopoietic cells to an animal, administration of nucleic acids encoding altered beta-chains to an animal, or using transgenic animals expressing genetically altered hematopoietic cells (in each case, the animal could be a human). However, there are no methods or working examples disclosed in the specification for administration of altered hematopoietic cells or isolated nucleic acids, or for creation of transgenic multicellular animals, that express the mutant receptor. Applicants previously argued that Example 4 teaches *in vivo* inhibition of phosphorylation by mutation of the binding motif; however, this example only teaches inhibition of phosphorylation in transfected HEK 293T cells in culture. Therefore, this example does not provide any teaching regarding *in vivo* cell survival in an organism.

However, the specification does not teach any methods or working examples that indicate the claimed nucleic acid is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the claimed nucleic acid into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express the claimed nucleic acid into the cell of an organism to treat disease. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express the claimed nucleic acid in the cell of an organism or be able to produce the encoded protein in that cell.

Furthermore, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated claimed gene is demonstrated to express the encoded peptide. There are also no methods or working examples in the specification indicating that a multicellular animal has the claimed gene "knocked out". The unpredictability of the art is *very high* with regards to making transgenic animals. For example, Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al (Blood

94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9 %) to "intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1, 2nd full paragraph; pg 3182-3183).

Due to the large quantity of experimentation necessary to introduce and express the claimed nucleic acid in a cell of an organism for therapy and to generate a transgenic animal expressing the disclosed protein, the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid in the cell of an organism to be able produce the encoded protein, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art that establishes the unpredictability of transferring genes into an organism's cells and the unpredictability of making transgenic animals, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

New rejections

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 77 and 79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 77 recites the limitation "the binding motif" in lines 1 and 2 (two recitations). There is insufficient antecedent basis for this limitation in the claim. Parent claim 73 has been amended to remove the recitation of "a binding motif". As such, the recitation of "the binding motif" in claim 77 lacks antecedent basis.

Claim 79 recites the limitation "the binding motif" in line3. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112, 1st paragraph, new matter

Claims 75, 76 and 79 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims contain new matter.

Claims 75 and 79 were each amended 2/2/07 to include the limitation that "at least two (2) amino acids at any positions from 598-603 are mutated" (claim 75) or "mutation of at least two (2) amino acids at any positions from 598-603 inhibits phosphorylation of the binding motif" (claim 79). On further consideration, neither the specification nor claims as originally filed provide a written description of the specific genus of "at least two" mutations in the recited binding motif (residues 598-603). The specification provides specific examples wherein 1, 3 or 6 residues of the binding motif are mutated. In each case, mutation of serine at position 601 is included. These three specific examples provide support for the genus of mutations recited in claim 1 wherein "the amino acid sequence ^{598}HSRSLP^{603} of the beta-chain comprises" both "one or more substitution mutations" and "a substitution mutation at the serine residue at position 601". Nowhere does the specification teach that "at least two" mutations should be made in the recited binding motif. Applicants' 2/2/07 remarks state, "[s]upport for these claim amendments can be found at, for example, the original claims and page 32, lines 25-27 of the specification". However, the original claims filed 3/14/02 do not contain any limitations with regard to mutations in a binding motif, let alone the number of said mutations. Furthermore, page 32, lines 25-27 of the substitute specification (filed 2/2/07) teach only that inhibiting phosphorylation may inhibit cell survival. Therefore, the specification as originally filed lacks support for the genus of "at least two" mutations recited in claims 75 and 79.

Claim 76 was newly introduced on 6/20/06 to include the limitation that "wherein the hematopoietic cell is a leukocyte". On further consideration, neither the specification nor claims as originally filed provide a written description of "leukocyte" as a subgenus of "hematopoietic cell" in the claimed methods. The specification refers only once to "hematopoietic cells" (pg 1, line 26). However, from this teaching it naturally flows that the other references to "cell survival" throughout the specification refer to "hematopoietic

cell survival". Applicants' 6/20/06 remarks state that support for new claim 76 can be found at page 33, lines 29-31; page 34, lines 1-2 and example 14 on page 57-58, lines 22-24. However, page 33, lines 29-31 refer only to preventing "cell survival of cancer cells or cell activation such as myeloid cell activation and may be useful for preventing or treating leukaemia such as acute myeloid leukaemia". With respect to cell survival (to which the current claims are directed), this teaching is directed only to "cancer cells" which is a different genus of cells than "leukocytes". Furthermore, even with respect to "cell activation", this teaching is directed only to "myeloid cells", which is a different subgenus of hematopoietic cells from "leukocytes". The subgenus "leukocyte" encompasses any white blood cell (WBC) whereas "myeloid cell" encompasses erythrocytes (red blood cells) and some but not all WBCs (e.g., T- and B-cells are lymphoid and not myeloid cells). Page 34, lines 1-2 and Example 14 refer only to "acute myeloid leukaemia", which is a specific type of cancerous myeloid cell that differs in scope from "leukocyte". Other working examples in the specification use "CTL-EN" cells (a type of cytotoxic lymphocytes) or "M1 cells" (derived from myeloid leukemia), none of which provide a written description for using the a subgenus with the scope encompassed by "leukocyte" in the claimed method. Therefore, the specification as originally filed lacks support for the genus of "lymphocytes" recited in claim 76.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

zch

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646